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Anatomical location of metastatic lymph nodes in anal carcinoma

Degree Project in Medicine

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Abstract

Master Thesis, Programme in Medicine

Anatomical locations of lymph node metastasis in the diagnosis of anal carcinoma

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Background: Squamous Cell Carcinoma of the Anal Canal (SCCAC) is a rare malignant disease, with an increasing incidence during the past decades. Standard regimen of treatment is chemoradiotherapy. During the past decade, Positron emission tomography–computed tomography (PET/CT) has been used more frequently for staging and therapy planning. The radiotherapy techniques of today are more conformal. This puts greater demand on the clinical target volume (CVT)- delineation, to prevent irradiation to healthy tissue and to minimize the risk of leaving micro metastases untreated.

Aim: The aim is to map the anatomical localization of regional lymph node metastases in anal cancer, in particular around iliaca externa, compare it with the literature and analyse whether today´s radiotherapy recommendations can be optimized.

Method: Patients listed under the diagnose code C21.X in the radiation therapy register during 2010 to 2017 were eligible for inclusion. Demographics were collected from the patient register Melior. The PET/CT lymph nodes were assessed by the nuclear imaging specialist. All data were collected depersonalized in a spreadsheet. The code key were kept separated and in a secure area.

Result: Out of a cohort containing 212 patients registered as C.21.X in the year 2010-2017, 166 patients with a verified anal cancer diagnosis and who had undergone a PET/CT were studied regarding anatomical locations of pelvic lymph metastasis. 48.9% of the 166 patients had positive lymph nodes at the time of diagnosis. 18.0% had positive mesorectal lymph nodes, 9.6% presacral lymph nodes, 32.5% inguinal lymph nodes, 7.2% lymph nodes around iliaca interna and 7.2% lymph nodes around iliaca externa. One patient with a <2 cm primary tumour had positive lymph nodes at the time for diagnosis. Furthermore, another patients with <2 cm primary tumour at time for diagnosis later developed a recurrence. No patients had positive iliacal lymph nodes at the time for recurrence.

Conclusion: The results suggest that adjuvant pelvic lymph node irradiated volumes may be

decreased in small tumours, and potentially decrease morbidity through more restrictive radiotherapy in SCCAC. When comparing the results with the literature, the rate of LNP was seen to be higher than studies using magnetic resonance imaging (MRI) and computed tomography (CT) but was consistent with studies using PET/CT.

Key words: Anal carcinoma, lymph node metastases, radiotherapy, PET/CT, MRI, IMRT, iliaca externa

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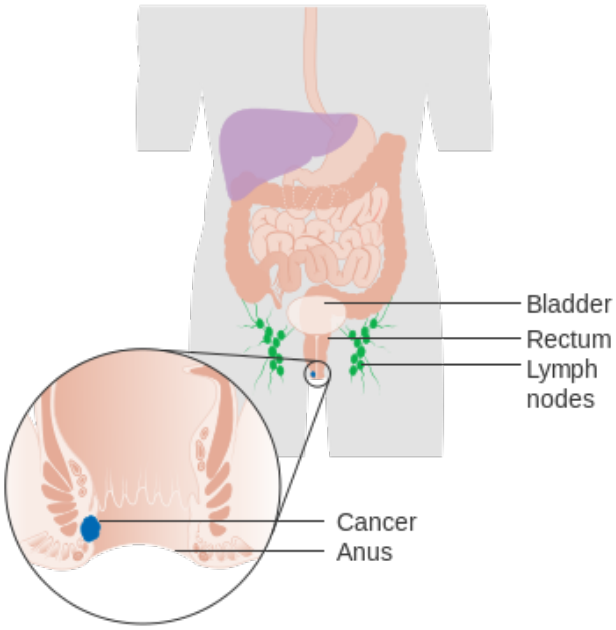
1. Introduction

Anal carcinoma is a neoplasm arising the anal canal. It often develops in the transformation zone between the columnar and squamous epithelium. Most tumours are squamous cell carcinoma (SCCAC) (65%) followed by transitional epithelium carcinoma (25%). More rare histologies are adenocarcinoma, basal cell carcinoma and melanoma of the anal canal (1). SCCAC, transitional epithelium carcinoma, basal cell carcinoma are managed in the same way while adenocarcinoma would be considered and treated as a distal rectal cancer.



Picture 1: Anatomical overview of anal cancer. Attribution: Cancer Research UK / Wikimedia Commons.

1.1 Incidence

Anal carcinoma is a rare malignancy, comprising 2 -2.5% of all gastrointestinal malignancies, with an annual incidence rate of around 1-2 per 100’000 and approximately 100 new cases per year in Sweden. The incidence increases after 40 years and reaches a peak in the sixth decade. The disease is more common among women, with a prevalence about 3-folds higher in women than in men. However, the incidence is increasing worldwide (2-4).

1.2 Etiology

Over the past century, there has been an increase in incident of this cancer. Reasons for this has been suggested to be higher prevalence of human immunodeficiency virus (HIV), human

papillomavirus (HPV) and changes in sexual behaviour (4).

1.2.1 Risk factors

Risk factors include infection with HPV, HIV, female gender, immunosuppression, receptive anal intercourse, cervical, vulvar or vaginal tumours and smoking (5).

1.2.2 Human immunodeficiency virus (HIV)

HIV has become one of the world´s most serious health issues with 36.7 million (6) living with the disease worldwide. The HIV-positive population is predisposed to develop malignancies due to infections by oncogenic viruses, including HPV. Several studies have found that anal cancer has a higher incidence rate in HIV-positive patients compared to the general population (34-100 vs. 1-2 per 100'000), with up to 100 per 100'000 in HIV-positive men who have sex with men (7, 8).

1.2.3 Human papillomavirus (HPV)

HPV infection is the major etiological basis for malignant development in the anal canal. It is a DNA-virus that commonly infects mucosal and squamous tissue, most often transmitted sexually. Majority of cases of anal squamous cell carcinoma are HPV-induced, up to 93,4% according to studies (9). There are numerous subtypes of HPV whereby persistent infection with so-called high-risk types, mainly HPV 16 (9), are associated with development of anogenital dysplasia (1, 10). Today, p16 immunostaining serves as a marker for HPV-oncogenesis. This is because of the ability of this method to find HPV pathognomonic koilocytos. P16 immunostaining has been a useful tool in diagnosing and grading HPV-associated neoplasia.

Tx	Primary tumor cannot be assesed
T0	No tumor present
Tis	Carcinoma in Situ
T1	Tumor sized less than 2 cm in greatest dimension
T2	Tumor sized 2 – 5 cm in greatest dimension
T3	Tumor sized more than 5 cm in greatest dimension
Nx	Regional lymph nodes cannot be assesed
N0	No regional lymph node metastasis
N1	Metastasis in perirectal lymph node(s)
N2	Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
N3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes
M0	No distant metastasis
M1	Distant metastasis present

Table 1
AJCC guidelines (11) for TNM staging of anal cancer.

1.3 Classification, the TNM-system

Depending on size and spread, the tumour is classified into stages, using the TNM-system. The now most commonly used classification is the 7th edition of the American joint Committee on Cancer (AJCC) (11) TNM staging.

1.3.1 T-stage

T-stage describes the size in cm of the primary tumour and whether the tumour invades adjacent organs, where T1 is the least locally advanced and T4 the most locally advanced. T4 is characterized by direct spread to organs/structures next to the tumour, such as the vagina, bladder, urethra and prostate gland. Invasion of the rectal wall, perirectal skin and/or sphincter muscles are not classified as T4.

1.3.2 N-stage

N-stage describes the spread to regional lymph nodes. The classification ranges from N0, no lymph nodes, up to N3, where bilateral inguinal and/or iliac or perirectal and inguinal/iliac lymph nodes are involved.

1.3.3 M-stage

M-stage describes whether distant metastases are present or not. The classification is divided into M0 with no distant metastases and M1, where distant metastases are present.

1.3.4 Prognosis

The main prognostic factor for survival and risk for recurrence is T-stage at clinical presentation, i.e. the size of the primary tumour. It has been shown that patients with T1-2N+ has similar or better prognosis compared to T3-T4N0 patients. Lymph node positivity is a poor prognostic factor as well, with a 5-year survival of 57% compared to 81 % for lymph node negative patients (12, 13). A study assessing 644 cases of anal cancer saw that patient with >5 cm primary tumour (i.e. T4) and N+ had worst prognosis (14). Other adverse prognostic factors are male gender and/or HPV-negativity.

Table 2

The AJCC prognostic system in SCCAC.

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	N0
II	T2	N0	M0
	T3	N0	M0
IIIa	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
IIIb	T4	N1	M0
	Any T	N2	M0
	Any T	N3	M0
IV	Any T	Any N	M1

1.3.5 Prognostic staging

The aim with TNM-classification is that it should reflect the prognosis. Depending on the TNM-classification, the patients are divided into several prognostic groups. This affects which treatment the patient will receive. The AJCC prognostic staging is described in table 2.

1.4 Diagnosis

The first symptom of SCCAC is often anal bleeding. Other signs may be painful defecation, a mass at the anal opening, narrowing of faeces and swollen lymph node in the anal and/or groin area (15). It may difficult to diagnose anal SCCAC in the early stages because frequently symptoms are similar to benign anal conditions, such as haemorrhoids. This can lead to both patient's and doctor's delay. First line examination is proctoscopy followed by palpation in anaesthesia (PIN). A biopsy is taken to verify the diagnosis histologically. Magnetic resonance imaging (MRI) and positron-emission tomography combined with computed tomography (PET/CT) are performed for TNM-stage classification. Detection of lymph node positivitiy (LNP) is important for planning radiotherapy doses and fields, thus puts a demand on accurate diagnostic techniques. Conventional imaging techniques has been MRI and CT, with a recently shift where PET/CT has been given higher importance.

Picture 2: A visable SCCAC. Attribution: Dr. K.-H. Günther, Klinikum Main Spessart, Lohr am Main

1.4.1 PET/CT

During the past decade, PET/CT) has been used more frequently for staging and therapy planning. In this nuclear medicine technique, Positron emission tomography (PET) is combined with computed tomography (CT). The trace element used in PET is 18-Fluorodeoxyglucose (F-18 FDG), which is a radiolabelled glucose analogue, is injected into a peripheral vein. When accumulating, it allows measurements of the rate of consumption of glucose, i.e. the metabolism. Since tumours have a higher metabolic rate, these can be distinguished from healthy tissue. PET/CT is important for radiotherapy target planning, providing the radiation oncologist detailed data about both the primary tumour extension and its relationship with adjacent organs as well as detailed information of lymph node involvement (16). An advantage of using PET/CT is that it can better detect distant metastasis, compared to conventional techniques, which gives it a

prognostic value (17, 18).

1.4.2 Weakness with PET/CT

F-18 FDG is not a cancer-specific agent, thereby making the interpretation difficult. Reasons to false positive results may be infection, inflammation in the pelvic/or lowers extremities region, post-operative changes, small tumours with low glycolytic activity and tumours near physiological uptake (19). This can potentially resulting in that benign lymph nodes are being classified as malignant. It is thus recommended that PET/CT is accompanied with other imaging modalities, such as MRI, or that a biopsy is performed on the suspected node, to minimize the risk of false positive findings. For example are often false positive uptake seen in the tonsils.

1.4.3 MRI or PET/CT?

It is well known among oncologist that there often is a discrepancy between MRI and PET/CT when imaging the small pelvis. Thus it is questioned whether the staging should be based on MRI or PET/CT. Today, the MRI-images and PET/CT images are shown, compared and discussed by both radiologists, nuclear imaging specialist and oncologist at clinical conferences.

A previous study showed PET/CT upstaged up to 37.5% of the patients and lead to modified treatment plans for up to 59.3% of the patients (17). This study suggested that PET/CT alters the staging and management in SCCAC in meaningful way. It should be stressed that up to 26.7% of the patients instead were downstaged. However, similar results has been seen in various studies (19-21)

Moreover, a meta-analysis from 2017 analysing 62 studies from 1982-2016 (12) came to the conclusion that there has been a 6.8% increase in LNP-frequency every 10th year, with the introduction of PET/CT.

1.5 Treatment

Today, the standard SCCAC treatment includes the use of concurrent chemotherapy and radiotherapy (chemoradiotherapy, CRT). Traditionally, surgery has been the choice of treatment until the mid-1980s. Previous research has established that CRT has better outcome, greater tolerability and often allows sphincter preservation (22, 23).

Recommended chemotherapy is a combination of mitomycin C and 5-fluorouracil.

Surgery is an option if there is residual tumour after CRT or as a treatment for recurrence.

The radiotherapy dose to the primary tumour is normally in the range of 45.0 – 60.0 Gy. In addition to the primary tumour, adjuvant radiation therapy is given to the inguinal, mesorectal, iliacal externa/interna, presacral and oburator lymph nodes to prevent the risk of Loco-Regional

Failure (LRF). LRF is defined by freedom from disease progression and recurrence. Adjuvant radiation therapy is given regardless of whether the patient has positive lymph nodes or not.

It is today questioned whether the adjuvant volumes may be reduced by omitting one or more of the lymph node stations in certain clinical situations. Today, radiotherapy-techniques such as intensity-modulated radiotherapy (IMRT), are increasingly more conformal. This means that more effective targeting and maximization of radiation dose can be achieved in the desired areas, so called Clinical Target Volume (CTV). Thanks to this, surrounding cancer-free tissue will be subjected to lower irradiation doses, potentially decreasing the morbidity by lowering both the short and long adverse effects. Thus, it puts greater demands on CVT delineation to minimize the risk of radiating on too small areas, leaving micro metastases untreated with an increasing risk of LRF.

The recommendation today is that they should be included (3, 24-27). As a consequence, there will be an increase in the administrated radiation burden, improving the LRF- control but with a higher risk for toxicity
However, there is still no consensus in the literature, with studies showing both that the adjuvant radiation may be decreased and other studies showing the opposite.
Wright, J et al .2010 (26) suggested that pelvic lymph nodes should be included in the CVT and common iliac nodes should be included as well in patients with advanced tumours and nodal stage. At the contrary, Kim et al. 2015 (28) did a retrospective journal study of 67 patients with anal cancer and came to the conclusions that adjuvant radiation therapy may be omitted for lymph node negative patients. Moreover, Das et al. 2007 (29) conducted a retrospective review of 167 patients who had underwent adjuvant radiotherapy, and showed a inguinal failure rate of 0% for 124 cases that were N0 at time for diagnosis.

In summary, it would be of great clinical importance if consensus could be reached in the question of the radiation burdens could be omitted or decreased in some clinical situations. This may spare the patients from both short- and long term toxicity, thus improving their quality of life (QoL). At the same time, it must be made sure that not too small areas are irradiated which would increase the risk of LRF. Thus appropriate clinical target volume (CTV) definitions are requested.

1.5.1 Adverse effects

Even though radiotherapy is effective on eradicating malignant cells, it is inevitable to not affect adjacent tissue and organs. Adverse effects can divide into acute adverse effect (within 3 months

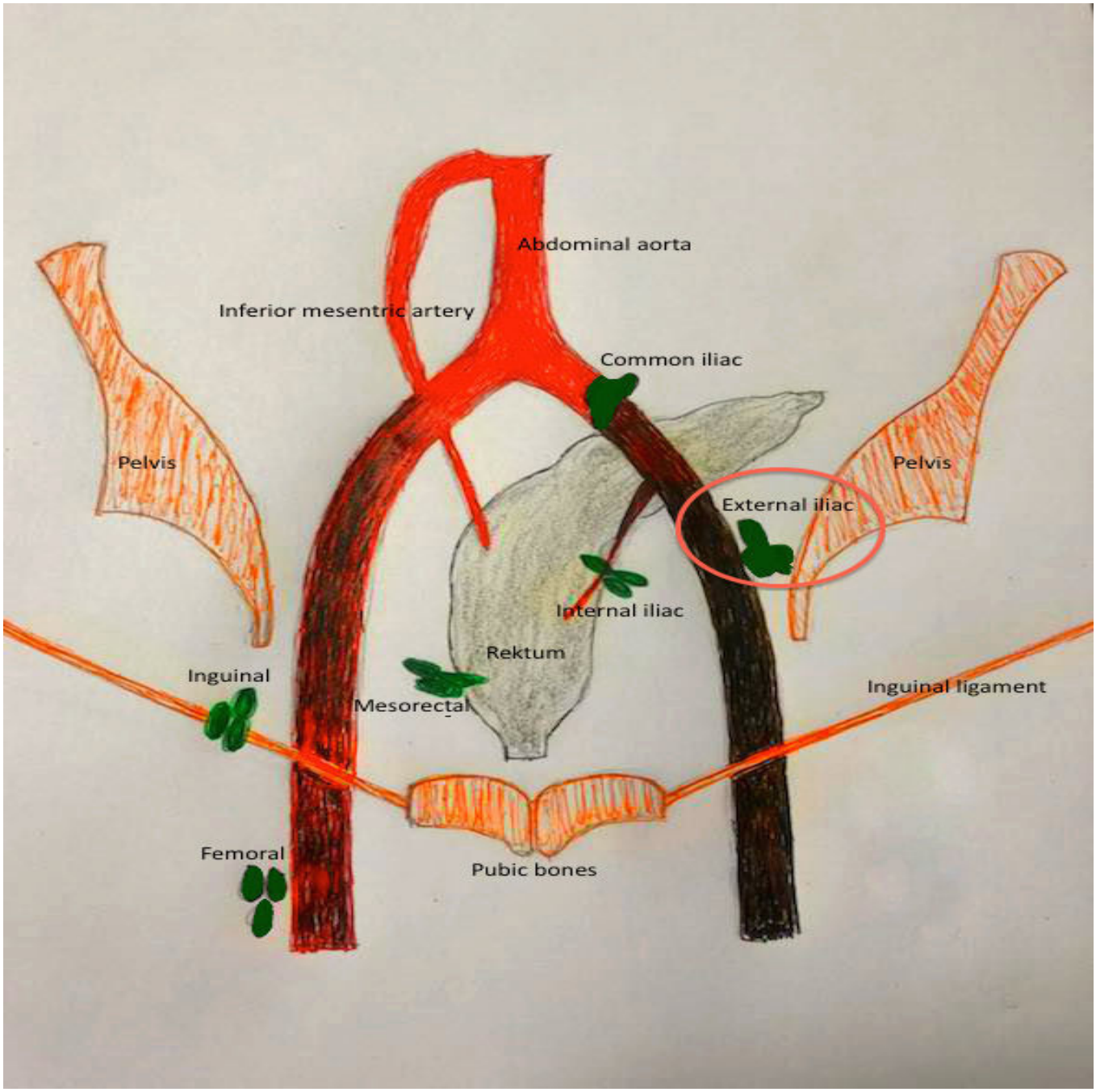
on start of therapy) and late adverse effects (appearing later than 3 months after start of therapy). Acute adverse effects are generally transient, while late adverse effects can show up long after the treatment and be more or less chronic. Acute gastrointestinal complications, such as diarrhea, are of a great concern due to the radiation sensitivity of the small intestine and its proximity to the CVT. Painful skin reactions are common and require often treatment with opioids. For the rectum and anus the adverse effects include rectal bleeding, proctitis, anal stenosis and fecal incontinence – which in some cases may even lead to the need of a permanent stoma. The genitals are often affected, which for men can lead to erectile dysfunction and for women vaginal shortening, stenosis and/or adhesions. For both sexes sterility is a likely outcome. It is of high importance that the patients quit smoking before the treatment since it can worsen acute toxicity and yield late toxicity (30, 31). It is important to minimize the risk for toxicity, since it may affect adherence to treatment.

1.6 Pelvic lymph node metastases

Spread from the primary tumour is manly via lymphatic vessels to regional lymph nodes and through direct extension, rather than haematogenous metastasis. Since the lymphatic drainage of the anorectum has both inguinal and mesenteric compounds, the pattern of spread can vary depending on the location of the primary tumour. Anal cancer is more likely to produce inguinal adenopathy and iliac adenopathy when the primary tumour is located near the anorectal junction. Regional lymph node stations are inguinal, internal iliac, external iliac, presacral, mesorectal and the obturator nodes. These lymph node stations are shown in picture 3 and 4 below.

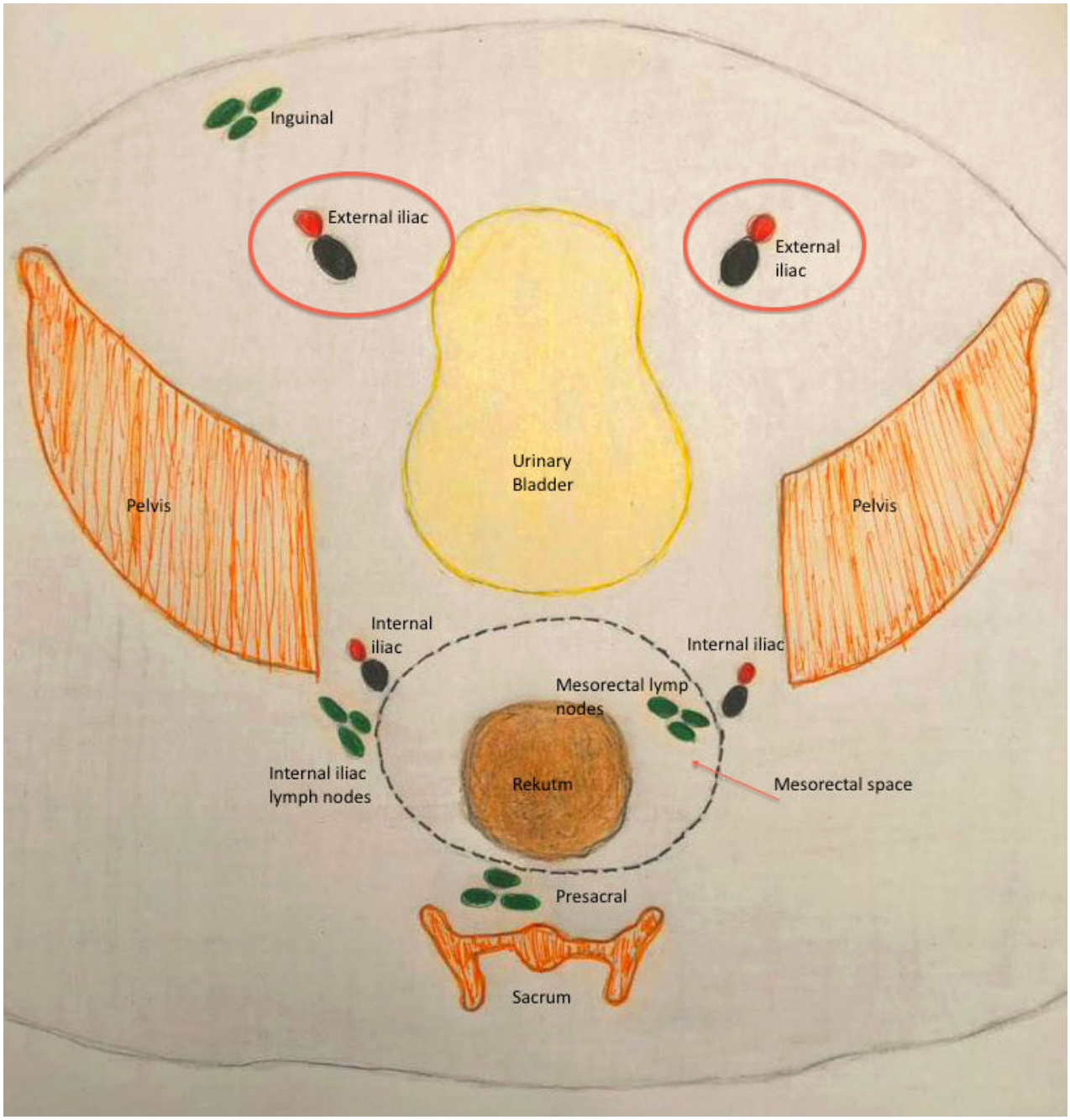
With the purpose to improve the target volumes definitions and provide a guidance in contour delineation for anal cancer, Australasian Gastrointestinal Trials Group (AGITG) developed an atlas and guidelines based on recommendations from a consensus working group (27). The article contained a recommended target volume atlas for anal cancer IMRT. It also covered MRI-images and anatomical definitions of locations of pelvic lymph node metastasis. In order to be as consistent and clear as possible, further anatomical definitions in this study will be based on AGITG's recommendations.

A retrospective study on PET/CT images from 2017 (32) saw that the most common location of regional lymph node metastasis are mesorectal with 30.6%, followed by inguinal with 17.3%. SCCAC often presents with local and regional involvement and distant metastases presents rather late in the disease course. The most common sites of distant spread are to the liver and to lungs (12, 15).



Picture 3

Coronal drawing showing lymph node stations relevant to anal cancer and some anatomical landmarks. External iliac lymph nodes are marked with a red circle.



Picture 4

Axial drawing showing lymph node stations relevant to anal cancer and som anatomical landmarks. Red cirkles= external iliac and internal iliac arteries. Blue cirkles= external iliac and internal iliac veins. External iliac are marked with a red circle.

The proportion of LNP seems to vary in studies, depending if it is based on MRI or PET/CT. A meta-analysis from 2017 analysing 62 studies from 1982-2016, showed a mean LNP proportion of 27.7%, with up to 37.1% for the more recent studies. The studies in the meta-analysis were based on both PET/CT images and MRI. Moreover, Gauthe et al 2017 (32) performed a retrospective study on 75 patients based on PET/CT images only and saw a LNP of 60.2%. It has been shown in previous studies that the use of PET/CT has altered the staging with 20-25%

compared to conventional imaging techniques; including MRI and CT (18, 21, 33) The introduction of new techniques may lead to an over diagnosis of lymph node spread, which in turn can lead to overtreatment and thus increase the treatment-related morbidity. Due to this, PET/CT is recommended to be complemented with other imaging modalities, or that a biopsy is performed on the suspected node, if reasonable, to minimize the risk of false positive findings (17)

1.6.1 Iliaca externa

There have been no previous detailed investigations of the lymph node distribution around iliaca externa. Therefore, there is unsecure of how beneficial it really is to irradiate this area. However, today lymph nodes around ilica externa et. interna has been recommended to be included in patients with T3 to T4 or/and N+ disease (29). Another reason to include this lymph station, and lymph nodes around iliaca interna, is that these lymph nodes may be difficult to control once the primary and mesorectal area has been irradiated, i.e. risk of overlapping treatment (34).

2. Aim

The primary objective with this study is to map the anatomical localization of pelvic lymph node metastases at primary diagnosis of anal cancer based on findings from initial work-up PET-CT, compare it with the literature and analyse whether today´s radiotherapy recommendations somehow be optimized.

In particular the purpose is to investigate the frequency of positive lymph node around iliaca externa to eventually demonstrate whether this area need to be included in the adjuvant volume.

Secondary objectives are to describe the treated patients demographics, survival and registered adverse effects.

Materials and methods

3.1 Population and data collection

A retrospective data analysis was performed on patients diagnosed with anal cancer (ICD-10 C.21) and treated with radiotherapy at Sahlgrenska University Hospital, Sweden, from 2010 to 2017. Patients listed under the diagnose code C21.X in the radiation therapy software Eclipse were eligible for inclusion. From these patients, two different study groups were constructed for the different parts of the study, based on the criteria described below.

For the ”final study group PET/CT images” inclusion criteria were a histologic verified diagnosis of anal cancer, primary diagnosis between 2010-2017 and that a staging or therapy-planning PET/CT should have been performed. PET/CT scans were performed before treatment.
The following anatomical locations were studied: mesorectum, presacral space, internal iliac, external iliac, inguinal and distant metastasis, using the anatomical definitions according to Ng et al., 2012 (27). The findings were based on the assessment in the written report by the nuclear imaging specialist and on an analysis of the images by the author.
The size of the primary tumour was measured, using the measurement tools in the radiology software, and pathological lymph nodes were registered. TNM staging was performed based on the written report by the nuclear imaging specialist and on the journal note from the PIN. When MRI images were available, these were also studied and a possible discrepancy with PET/CT was noted. The American Joint Committeeon Cancer TNM system, 7th edition (11) was used for staging.

Demographics, recurrence and adverse effects related to radiotherapy were studied for the “final outcome group”. For this part of the study the inclusion criteria were a diagnosis of anal cancer, primary diagnosis before 2010 and that the patients attended the follow-up controls in the hospital. The patients were studied through analyses of their journals in the administrative program “Melior”. Following parameters were studied: sex, age, survival, date of start for radiotherapy, histology, TNM-classification, reported early adverse effects (within 3 months from the start of radiotherapy), reported late adverse effects (more than 3 months from the start of radiotherapy), frequency of recurrence and the date when recurrence was verified. If the patients were dead, the date of death, cause of death and age at death were studied as well. The cause of death was based on the death certificate. Overall survival (OS) was measured from the date for start of radiotherapy to the date of death from any cause. Only recurrences with verification, radiological or

histological, were included. The studied acute adverse effects were divided into the following subgroups: infection, blood, urinary tracts (both higher and lower), skin, genitalia, anus, pain, cardiovascular and others. For late adverse effects the subgroups were: skeleton, anus, genitalia, wound, pain, fecal incontinence, urinary tracts, stoma and others. Skin reactions were included in the cases were the patient was forced to interrupt treatment, and pain were included when it required higher doses of analgesics than expected. Diarrhea was not recorded, since it needs to be graded and the studied medical records are not suitable for this. For the patients who had to interrupt the radiotherapy, the reached dose at time for interruption was recorded.

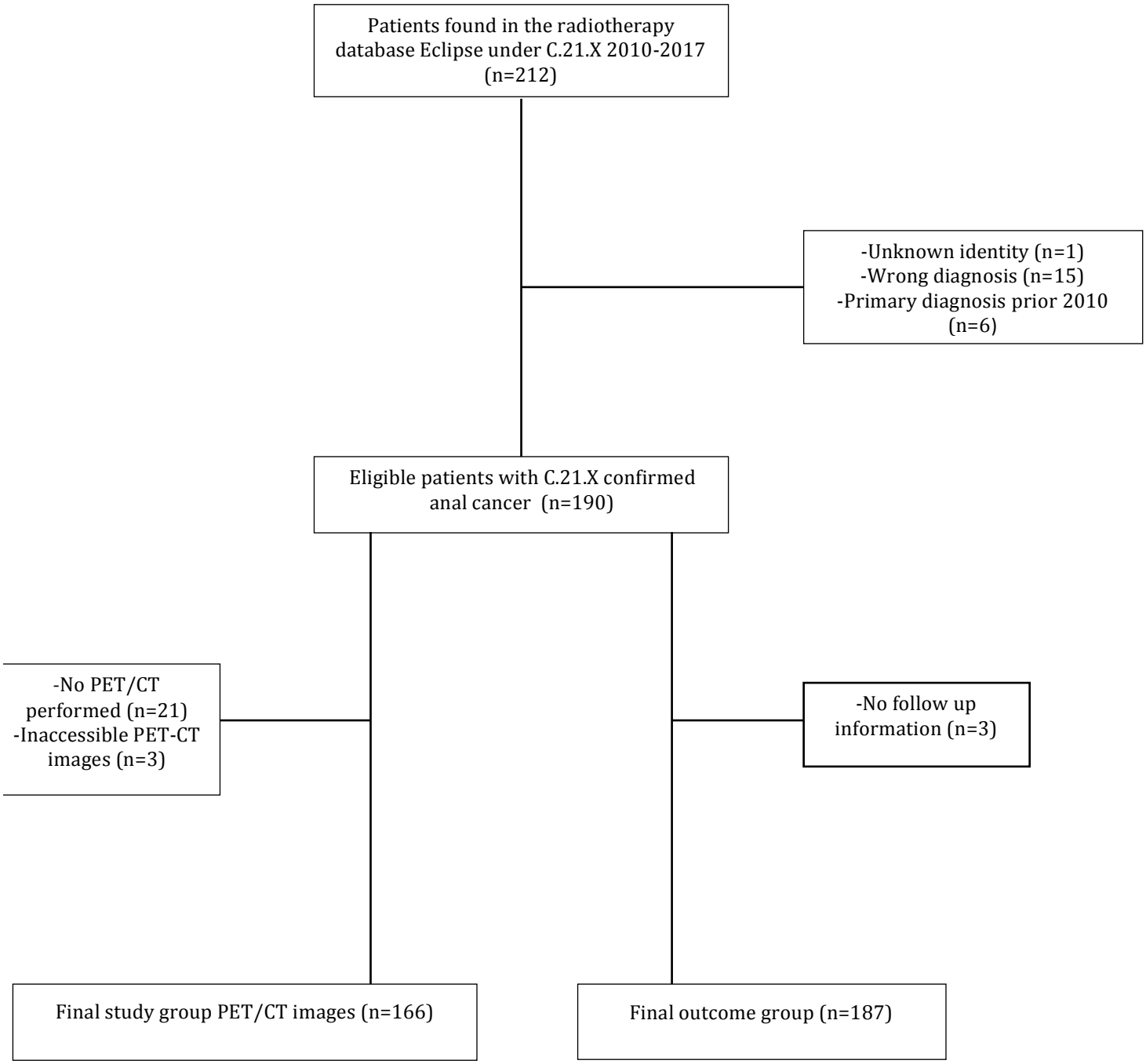
All data in the study were collected depersonalized in a spreadsheet. The code key was kept separated and in a secure area.

3.2 Statisical methods

Statistical analysis was performed using SPSS version 25 and Excel 2011. To calculate statistical significance and difference among proportions, a Chi-squared test was applied. For small sample sizes, Fisher's exact test was used. Kaplan-Meier analyses were done for the over-all survival data.

3.3 Ethics

This study was part of a larger retrospective radiotherapy project, which is approved by the Regional ethical review board in Gothenburg, 2015-02-11. The diary number is 030-15.



Consort diagram 1

The study populations

4. Results

4.1 The study populations

4.1.1 Final study group PET/CT images

A total of 212 patients were identified as C21.X in radiotherapy planning software Eclipse. Out of the 212 patients, 15 were excluded due to wrong diagnosis (14 rectal cancer, 1 pancreas cancer), 6 patients with primary diagnosis before 2010, 1 patient with unknown identity, 21 patients with no PET/CT and 3 patients with inaccessibility to PET/CT images. The remaining 166 patients were finally included in the *final study group PET-CT images*.

4.1.2 Final outcome group

Out of the 212 patients in the primary group, 15 were excluded due to wrong diagnosis (14 rectal cancer, 1 pancreas cancer) 1 with unknown identity, 6 patients with primary diagnosis before 2010 and 3 had no follow up information. The remaining 187 patents were included in the *final outcome group*.

The two studied populations are described in the consort diagram 1 above.

4.2 Pelvic lymph node metastases

Of the 166 patients in the final PET/CT study group a total 50% (n=83) had some metastatic spread, LNP and/or distant metastases, present at the time of diagnosis (N1-N3 or/and M1). Out of these, 21.7% (n=18) were men and 78.3% (n=65) were women. This means that out of the 36 men in the final group, 50% had metastatic spread. For the 130 women, also 50% (n=65) had metastatic spread.

Moreover, 48.9% (n=81) had LNP (N+) at the time for diagnosis. The most common anatomical location according to the PET/CT images was seen to be inguinal with 32.5% followed by mesorectal with 17.3%. When divided by gender, chi-squared test in SPSS could not show any statistical significant difference between the genders regarding the subsite specific locations of pelvic metastasis. The anatomic sites for pelvic lymph nodes for the 166 patients are described exactly in table 3 below. The 83 patients with metastatic spread are further grouped into their TNM-stage, depending on their site of spread.

The 166 patients in the Final study group PET/CT images are divided by their T-stage and N-stage in table 4 below.

Of the 81 patients with LNP, 1 had stage T1 compared with 33 T2, 25 T3 and 22 T4. Pearson's correlation coefficient, done in Excel, gave Rho=0.52. Further, a chi-square test done in SPSS gave p –value <0.05, thus indicating for a positive correlation between size of tumour and the risk of metastatic spread.

Table 3

The anatomical locations of the pelvic lymph nodes for the 166 studied patients in the PET/CT group at the time of diagnosis. The table shows number of patients in each stage for the studied lymph nodes station. The patients with metastatic spread, N+ and/or M1 (n=83) further are grouped into their TNM-stage.

Pelvic lymph node station	Total (n=166)	Men (n=36)	Women (n=130)	T1	T2	T3	T4	N0	N1	N2	N3	M1
Local disease (N0)	83 (50.0%)	17 (47.2%)	68 (52.3%)									
Mesorectal	30 (18.0%)	5 (13.9%)	25 (19.2%)	0	10	8	12	0	13	13	4	3
Presacral	16 (9.6%)	2 (5.6%)	14 (10.8%)	0	4	4	8	0	5	6	5	3
Inguinal	54 (32.5%)	14 (38.9%)	40 (30.8)	1	22	18	13	0	0	32	22	6
External iliacal	12 (7.2%)	4 (11.1%)	8 (6.2%)	0	4	1	7	0	0	6	6	3
Internal iliacal	12 (7.2%)	3 (8.3%)	9 (6.9%)	0	4	3	5	0	0	8	4	2
Distant metastasis	10 (6.0%)	1 (2.8%)	9 (6.9%)	2	1	3	4	2	0	4	4	

Table 4

The 166 patients in the final study group PET/CT divided by their T-stage and N-stage

(n)	T1	T2	T3	T4
N0	18	37	18	12
N1	0	7	3	6
N2	0	19	15	8
N3	1	7	7	8

6 % (n=10) of the patients had distant metastasis (M1) present at the time of primary diagnosis. Out of these 10 patients, 8 patients had both LNP and distant metastasis. Moreover, 2 patients with distant metastasis were lymph node negative. They had stage T1 and T2 respectively.
The most common locations for distant metastasis were liver (n=3) and paraaortic lymph nodes (n=3). The anatomical sites for the distant metastasis, both at time of primary diagnosis and at the time of recurrence, are described in table 5 below.

Table 5

The anatomical location for distant metastasis at the time of primary diagnosis (n=10) and at the time for recurrence (n=16). One patient had metastatic spread in both lungs and iliaca communis at the time of diagnosis. two patients had metastases in liver +lung and one patient each had spread in lung + skeleton and liver + paraaortic lymph nodes.

Location of distant metastases	Number of patients (n) at the time of primary diagnosis	Number of patients (n) at the time of recurrence
Liver	3	7
Paraaortic lymph nodes	3	3
Skeleton	1	3
Iliaca communis	1	1
Lung	2	5
Uterus	1	0
Scrotum	0	1

4.3 TNM-stages

The TNM-stages, based on the written report by the nuclear imaging specialist for the total 166 patients in the PET/CT group are presented in the table below. The most common stage was T2N0M0, accounting for 21.7% of the patients (n=36). It is followed by T2N2M0 and T3N3M0, with 11.4% of the patients each (n=19). The third most frequent stage was T3N2M0 with 7.2% of the patients (n=12). 46.4% of the patients presented a locally advanced tumour (T3 or T4).
Gender difference was calculated using Chi-squared test in SPSS. P-values and the distribution of the stages are presented in table 6 below.

Table 6

The distribution of the TNM-stages for the 166 patients. The p-value or the gender difference is shown in the table and marked with an asterix when significant.

Stage	PET-CT group (n=166)	Women (n=130)	Men (n=36)	P-value
T1	19 (11.4%)	15 (11.5%)	4 (11.1%)	0.845
T2	70 (41.6%)	52 (40.0%)	18 (50.0%)	0.246
T3	43 (25.9%)	32 (24.6%)	11 (28.2%)	0.472
T4	34 (20.5%)	31 (23.8%)	3 (7.7%)	0.041*
N0	85 (51.2%)	68 (52.3%)	17 (47.2%)	0.589
N1	16 (9.6%)	15 (11.5%)	1 (2.8%)	0.115
N2	42 (25.3%)	32 (24.7%)	10 (27.8%)	0.699
N3	23 (13.9%)	15 (11.5%)	8 (22.2%)	0.042*
M0	156 (94.0%)	121 (93.1%)	35 (97.2%)	0.355
M1	10 (6.0%)	9 (6.9%)	1 (2.8 %)	0.355

4.4 Recurrence

Out of the 187 studied patients in the Final outcome group (n=187) 17.6% (n=33) had a relapse, out of which 8 were men and 25 women. Regarding recurrence, no statistically significant difference was found between the genders (p-value 0.598).

Out of the 33 patients with a verified recurrence, 33.3% (n=11) later died from the disease. This means that out of the total 16 patients who later died from the disease, 68.8% had a recurrence. There were eleven anal carcinoma registered deaths in the recurrence group of 33 patients compared to only five anal carcinoma registered deaths from the 154 patients who did not have a recurrence. (p-value< 0.05).

Both these data sets were analyzed with a chi-squared test in SPSS.

The site of recurrence varied from the local area to regional pelvic lymph nodes to distant metastasis. For 2 of the 33 patients with recurrence, conclusions could not be drawn due to lack of PET/CT; following results are based on the remaining 31 patients. 32.3% (n=10) had a local relapse with no regional or distant metastases present (N0 and M0). 32.3% (n=10) had positive regional lymph node metastasis; out of these 19.4 % (n=6) had positive inguinal lymph nodes, 9.7% (n=3) had positive mesorectal lymph nodes, and 3.1% (n=1) had positive presacral lymph nodes. It should be mentioned that no patient had a recurrent positive lymph node around iliaca externa and iliaca interna. The anatomical locations for the pelvic metastasis at the time of recurrence are described in table 7 below.

Table 7

The anatomical locations of the pelvic lymph nodes for the 31 patients with verified recurrence. The patients with metastatic spread at time of recurrence (n=21) are grouped into their TNM-stage, based on the PET/CT image at the time of primary diagnosis. The result in the study is showed both in percentage and number of patients out of the total 31 (x/31). It should be mention that no patient developed a recurrence around iliaca externa and iliaca interna.

Pelvic lymph node station	Number of patients (n=31)	T1	T2	T3	T4	N0	N1	N2	N3	M1
Local disease	32.2% (10/31)	1	4	2	3	4	1	3	2	1
Meosrectal	9.7% (3/31)	0	0	0	3	0	1	0	2	1
Presacral	3.1% (1/31)	0	1	0	0	1	0	0	0	1
Inguinal	19.4% (6/31)	0	2	2	2	2	0	1	3	0
Iliaca externa	0	0	0	0	0	0	0	0	0	0
Iliaca interna	0	0	0	0	0	0	0	0	0	0
Distant metastasis	51.6% (16/31)	1	5	4	6	7	1	5	3	2

16.1% (n=5) experienced both regional and distant metastasis at the time for the relapse and 51.6% (n=16) had distant metastases. 50% (n=5) of the patients with distant metastasis at the time of primary diagnosis developed recurrence. The most frequent sites for distant metastasis were liver (n=7) and lungs (n=5). The anatomical distribution of the distant metastasis at the time of recurrence is shown in table 5 above.

The time interval from the date for start of radiotherapy to the date for relapse ranged between 4-57 months. The mean value was 17 months and the median was 10 months.

4.5 Demography

4.5.1 Gender

The gender distribution is shown in table 8.

Table 8

The gender composition for the final study group PET-CT images, the final outcome group and the patients with recurrence

	Men	Women
Final study group PET-CT images (n=166)	36 (20.9%)	130 (79.1%)
Final outcome group (n=187)	39 (20.7%)	148 (79.3%)
Recurrence (n=33)	8 (24.2%)	25 (75.8%)

4.5.2 Age

Age, studied for the total 190 patients with an anal cancer diagnosis 2010-2017, ranged from 29 years up to 94 years. The mean value was 64.5 years and the median was 64 years. The most frequent age interval was between 66-70 years with 34 patients, followed by 31 patients between 56-60 years. For women the range was 35-94 years. The mean value was 64.6 years and the median was 64 years. The range for men was 29- 88 years with a mean value of 63.8 years and a median of 64 years. Most women got their diagnosis between 51-55 years (n=25). For men, the most common age interval was 66-70 years (n=12). The age composition for the total population is illustrated in figure 1a and divided by gender in figure 1b.

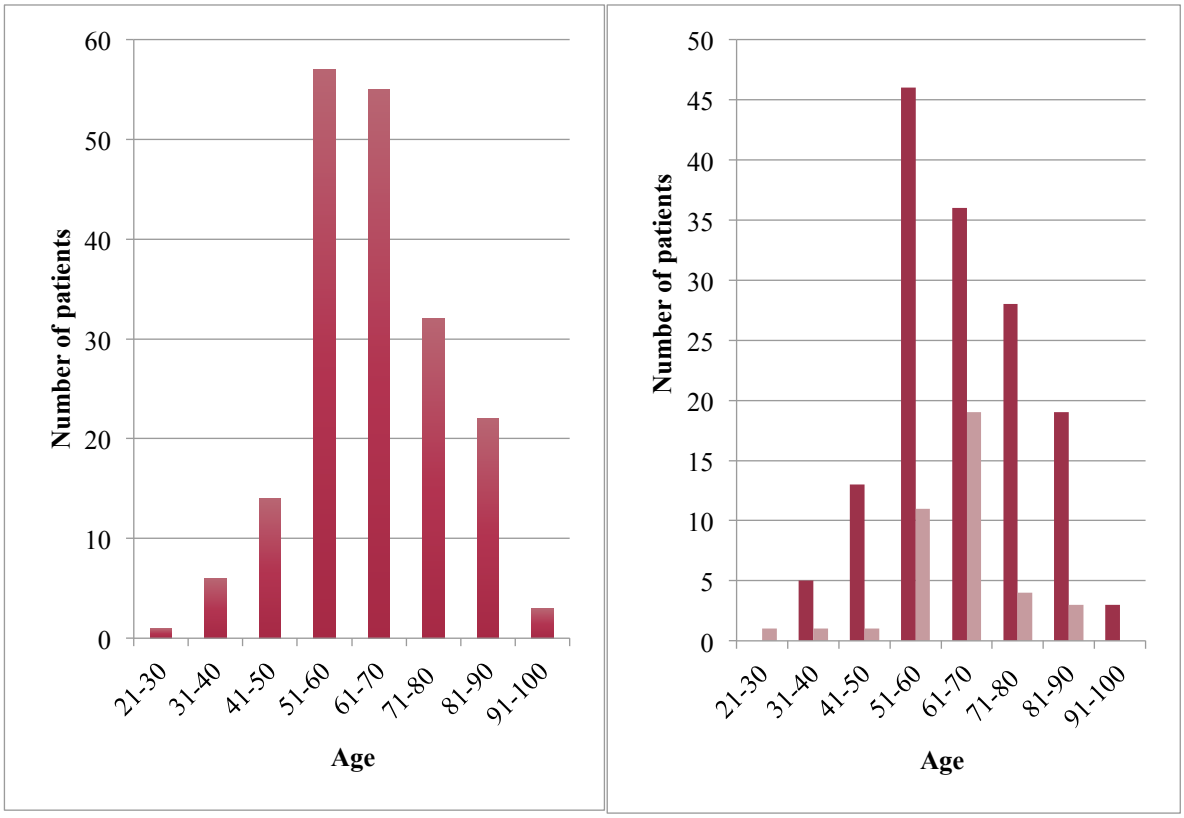


Figure 1a + 1b

Figure 1a (left) shows the age distribution in 10-years interval for the total 190 eligible patients diagnosed with anal cancer 2010-2017. Figure 1b (right) shows the age distribution divided by gender, where dark red=men, light red=women.

4.5.3 Histology

For the 187 patients with anal cancer in the final outcome group, the predominant cell types were squamous cell 96.9% (n=181) followed by basaloid 3.1% (n=6).

4.5.4 Survival

For the 187 patients in the final outcome group 19.8% patients had passed away (n=37). Out of these, six patients had an unknown cause of death. For the remaining 31 patients, 16 died due to anal cancer during the study period, which counts for 8.6% of all the patients in the final study group and 42.2% of the total deaths. The age of death ranged between 30-93 years. The mean value was 72.2 years and the median was 73 years. For women, the mean value was 77.4 years and for men 63.5 years.

For the patients who died of anal cancer, 10 were women and 6 were men. This means that out of the total 39 men, 15.4% died of anal cancer. For women, this number was 6.8%. The over-all survival is shown in figure 2 and table 9 below. Even though our results suggest that men have a lower survival, a chi-square test in SPSS showed no statistical significant difference between the genders, p-value 0.087.

Total, 27 patients died from some kind of malignancy. Beyond the 16 patients with anal cancer, six patients died from lung cancer and one patient each died from rectal cancer, colon cancer, vulvar cancer, myelodysplastic syndrome and malignant melanoma. For the remaining patients, three died from chronic obstructive pulmonary disease and one patient each died from heart failure and Alzheimer´s disease.

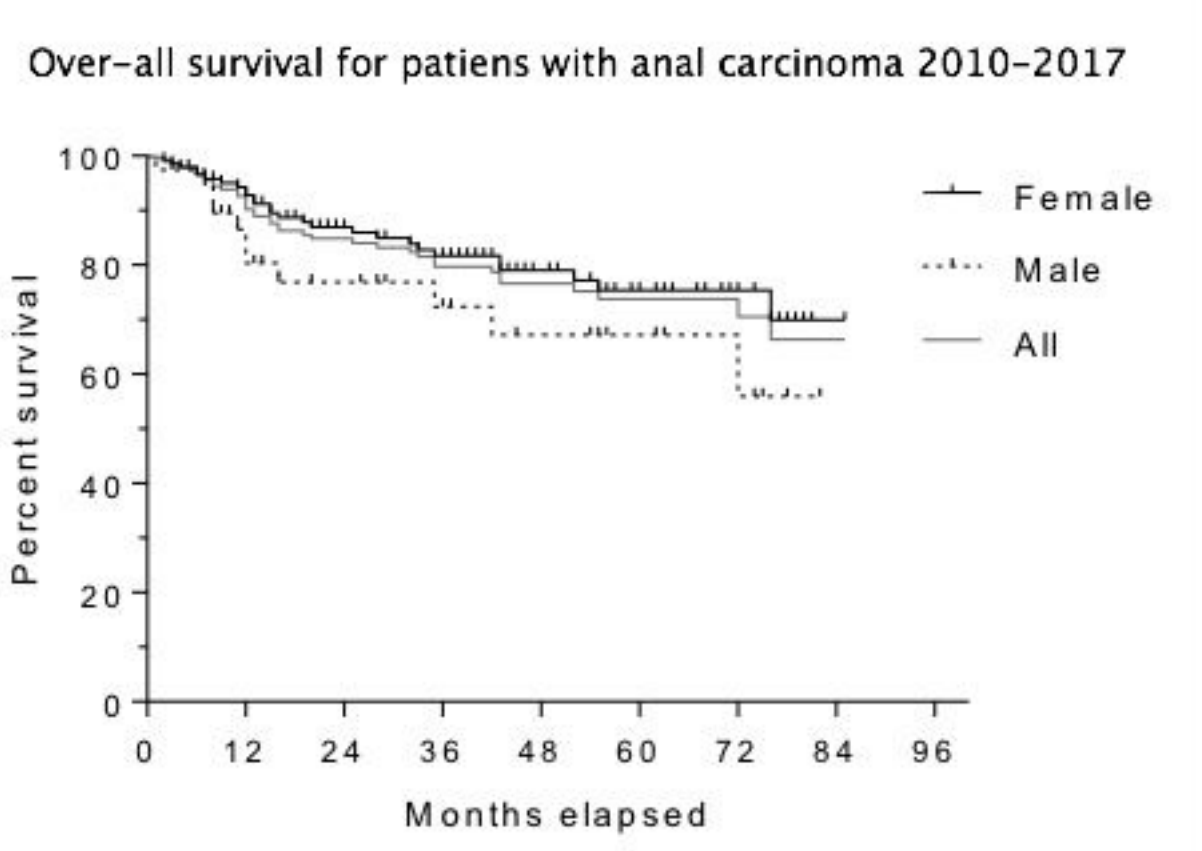


Figure 2

Kaplan Meier-plotter for the over-all survival of anal carcionoma for the 187 patients 2010-2017. Each pile in the curve corresponds to a living patient.

Table 9

The overall survival in percentage for the 187 patients with anal cancer between 2010-2017.

	All	Women	Men
1 year survival	90%	93%	80%
2 year survival	85%	87%	77%
3 year survival	80%	82%	72%
5 year survival	74%	75%	67%

4.6 Adverse effects

4.6.1 Acute adverse effects (>3 months)

For 25.1% (n=47) of the 187 studied patients we found reported acute adverse effects related to their radiotherapy-treatment. None of the patients died within 2-3 months after finished radiotherapy. The most frequent documented acute adverse effect was radiation dermatitis, (n=34) out of which 25 patients developed a secondary infection in the skin of the irradiated area (virus, bacteria or fungi). In total, skin reactions counts for 72.3% of the 47 patients with acute adverse effects, and 18.2 % of the patients in the final outcome group. In terms of adherence to treatment, 12 patients, who count for 25.5% of all the patients with adverse effects and 6.4 % of all the patients, had to interrupt radiotherapy-treatment in advance. The main reason was due to radiation dermatitis (n=9) followed by infections (n=3). The radiation doses at the time for interruption varied between 46 Gy – 58 Gy, with mean value of 54 Gy and median of 56 Gy. All of these patients were planned for a radiation dose of 60 Gy to the primary tumour in the anal canal. A detailed description of the reported adverse effects and number of patients affected are found in table 10 below.

Table 10

Table showing the number of patients and type of documented acute adverse effect for the total 47 affected patients. The percentage is shown for the 47 patients and for the total 187 patients in the final outcome group. Patients could have more than one adverse effect.

Subgroups	Total number of patients	Number of patients + type of adverse effect	Percent (%) of the patients with early adverse effects (=47)	Percent (%) of the total studied patients (n=187)
Infections	2	2 sepsis	4.3	1.0
Blood	3	1 transfusion-requiring anal bleeding, 1 thrombocytopenia, 1 neutropenia	6.4	1.6
Urinary tracts	6	2 catheter, 2 urethritis, 1 Urinary retention (need of catheter) 1 hydronephrosis (need of nephrostomy)	12.8	3.2
Skin	34	9 radiation dermatitis, 25 moist infection	72.3	18.2
Genitalia	4	2 erectile dysfunction, 1 balanitis, 1 rectovaginal fistula	8.5	2.1
Anus	2	1 anal stenosis, 1 anal abscess	4.3	1.0
Pain	2	2	4.3	1.0
Cardiovascular	4	2 deep vein trombosis, 1 pulmonary embolism, 1 myocardial infarction	8.5	2.1
Others	2	1 SIADH (syndrome of inappropriate secretion of ADH) 1 ileus	4.3	1.0
Patients who had to interrupt treatment:	12	9 infections, 3 skin reactions	25.5	6.4

4.6.2 Late adverse effects (<3 months)

For 36.9% (n=69) of the 187 patients in the final study group we found reported late adverse effects. Most often the anus was affected, with 42.0% (n=29) of all the patients with adverse effects and 15.5% of all the patients in the study group. Out of these 29 patients, 22 developed anal stenosis. The second most common was that the genitals were affected, with 30.4% (n=21) of all the patients with adverse effects, and 11.2% of all 187 studied patients. Nine men developed erectile dysfunction and for the women, six developed shortening of the vagina, six vaginal stenosis and four vaginal adhesions. As a consequence, one of these women was not able to perform penetrating intercourse. Eight patients had long-lasting problems with pain and one patient had needed rectum amputation due to this. So far 5.3% of the patients in the final outcome group have needed a stoma and the main reason for this was fecal incontinence. A detailed description of the reported late adverse effects and number of patients affected can be seen in table 11 below.

Table 11

Table showing the number of patients and type of documented late adverse effect for the total 69 affected patients. The percentage is shown for the 69 patients and for the total 187 patients in the final outcome group. Patients could have more than one adverse effect.

Subgroups	Total number of patients	Number of patients + type of late adverse effect	Percent (%) of the patients with late adverse effects (=69)	Percent of the total studied patients (n=187)
Skeleton	16	5 fissure, 9 fracture, 2 radiation-induced skeletal changes	23.2	8.6
Anus	29	22 stenosis, 6 proctitis, 1 prolapse	42.0	15.5
Genitalia	21	9 erectile dysfunction, 6 abbreviated vagina, 6 vaginal stenosis, 1 rectovaginal fistula, 4 vaginal adhesions	30.4	11.2
Wound	9	9	13.0	4.8
Pain	8	8	11.6	4.3
Blood	5	4 anal bleeding, 1 bone marrow degreasing	7.2	2.7
Fecal incontinence	10	10		5.3
Urinary tracts	1	1 urinary incontinence	1.4	0.5
Stomia	10	1 pain, 6 fecal incontinence, 2 wound, 1 proctitis	14.5	5.3
Other	2	2 lymphedema	2.9	1

5. Discussion

5.1 Pelvic lymph node metastases

Today, it is questioned whether the adjuvant volume can be decreased by omitting one or more of the pelvic lymph node stations in certain clinical situations. The recommendation today is that they should be included. As a consequence, there will be an increase in the administrated radiation burden, improving the LRF- control but with a higher risk for toxicity. With this background, this study aimed to map the anatomical location of pelvic lymph nodes in SCCAC –patients, based on PET/CT, to see whether today´s recommendations for radiotherapy somehow can be optimized. From the results above, some points can be made.

Firstly, the result implies that adjuvant irradiation may be decreased in the smallest local tumours. As seen in table 3, it was noticed that out of the 81 patients with LNP, only one patient had a stage T1 tumour at the time of diagnosis, compared to the fairly even distribution between T2-T4. This implies that adjuvant pelvic irradiation volumes might be reduced for the smallest tumours (T1). That would potentially lower the risk for morbidity in SCCAC patients. This result is comparable with previous studies. For example, Ortholan et al. 2012 (3) suggests that adjuvant pelvic lymph node irradiation should be recommended for stage T3-T4 while only considered for early stage tumours. However, that study had some limitations. For example, the involvement of pelvic lymph nodes was assessed by CT, and not MRI or PET/CT. Gerard et al. 2001 (34) emphasized that the risk of metastatic spread increases with greater size of the primary tumour, T-stage. This relation was also seen in this study, p-value <0.05. Tumour size >5 cm has been reported to be a stronger independent prognostic factor (14) than lymph node positivity, again consistent with the results in this study. This further supports the idea that adjuvant irradiation may be decreased in the smallest tumours.

Secondly, a higher frequency of LNP seems to be seen in studies based on PET/CT compared to studies based on conventional techniques (MRI).
In this study a LNP frequency of 48.9% (n=81) was noticed. Gauthe et al. 2017 (32) observed a frequency of LNP of 60.2% when retrospectively studying PET/CT images.
Moreover, a meta-study analysing 62 studies, from 1982-2016 showed a mean LNP proportion of 27.7%, with up to 37.1% for the more recent studies were seen (12). It can be mentioned that this study observed an LNP frequency of about 15% for the studies during the 1980s. These studies were based on MRI. Thus, it seems that our PET/CT-based study shows a higher frequency of LNP compared to the MRI-based studies. This finding is consistent with that of Gauthe et al 2017

(32) that noticed a higher frequency of LNP as well. It is possible, therefore, that PET/CT studies report a higher frequency of positive lymph nodes compared to MRI/CT studies. This suggestion are in are in agreement with those obtained by Bhuva et al. 2012 (35) which concluded that PET/CT alter staging in anal cancer for a significant population. Furthermore, Sekhar et al. 2017 (12), came to conclusion that there has been a 6.8 % increase in LNP proportions every 10^{th} year during the past decades. However, it may be difficult to draw conclusions since only a few studies today are based alone on PET/CT.
Moreover, it is well known that there often is a discrepancy between MRI and PET/CT. For example, 26 patients in this study had a difference of susceptible lymph nodes between these two techniques, both down staging and upstaging. This difference has been noticed in various previous studies; and there is still no consensus whether the staging primary should be based on the MRI or PET/CT (17, 35). Further research is needed in this area.

Thirdly, our result indicates there may be a difference between some anatomical subsites.
The most common location of spread in our study was seen to be inguinal with 32.5% followed by mesorectal with 17.0%. This result is in contrary to Gauthes et al. 2017 (32) where mesorectal was seen to be the most common location of spread. However, this can be questioned since that study had broader inclusions for positive lymph nodes than our study. Moreover is there few studies based only on PET/CT. Thus, we cannot exclude that that there may be some difference between the anatomical subsites.

Fourthly, iliaca externa is suggested to stay as a part of the adjuvant irradiation.
We noted that 7.2% of the patients had positive lymph nodes around iliaca externa. No previous detailed investigations of the spread around iliaca externa have been done. Together with 7.2% around iliaca interna, a total of 14.2% of the patients had some iliacal spread. With this follows a risk for micrometastasis. Thus, we cannot draw any conclusions to omit iliaca externa. Instead, it is suggested that this lymph node station should stay as a part of the adjuvant pelvic lymph nodes, at least for the patients with bigger tumours (T2+). This is also consistent with recommendations from previous studies (29). An other reason to include this lymph station, and lymph nodes around iliaca interna, is that these lymph nodes may be difficult to control once the primary and mesorectal area has been irradiated, i.e. risk of overlapping treatment (34). Hopefully in the future, this result may open up for further research about metastasic spread around iliaca externa, which is requested before any changes of todays recommendations can be done.

Fifthly, PET/CT seems to better detect distant metastasis compared to conventional techniques. Distant metastases are present late in the disease, 6.0% (n=10) of the patients in the study had distant metastases at the time of diagnosis. This was higher than expected from the literature, for example in a study of 1266 patients (2), based on CT and MRI, 1.8% of the patients had distant metastasis. Gauthes et al. 2017 (32) saw a frequency of 5% of distant metastasis based on PET/CT. A possible explanation for this might be that PET/CT has been seen to be able to detect distant metastasis missed by conventional imaging, in up to 4.7% of the cases, seen in studies (17). This has a prognostic value. Distant metastasis is associated with LNP (23), as seen in the current study were 8 of the 10 patients with distant metastasis also had LNP. Surprisingly, 2 patients were seen to have distant metastasis but no regional metastasis, table 3. It can here be questioned whether these really were metastases from anal cancer or if this was a completely other malignancy.

Finally, while there was no different in localization of the lymph node metastases based on gender, there was a difference in size and stage of regional spread.
Gender was seen to have no effect on the localization of the lymph node metastases. However, there seems to be a statistically significant difference that women have more locally advanced tumours (T4) at the time of diagnosis, compared to men, (p-value 0.041) while men more often has more advanced lymph node spread (N3) (p-value 0.042), as seen in table 6 above. This could suggest that men has more aggressive tumours while women has more slow growing local tumours that tend to spread later in the disease course. Of course could this result be seen as a consequence of mass significance but since a similar relationship has been seen in previous literature, it is not impossible that it is correct. Male gender is a well-known adverse prognostic factor (14). Even though the study observed that a greater percentage of the men died compared to the women, a statistical significance could not be seen. Also, incidence for men peaked at an older age, as seen in table 1b above. This opens up for discussion if there may be an etiological difference of the tumours between the genders. As a notification, could it here be discussed if there is a difference of P16-status between the genders, and that women might have a higher incidence of HPV-positive tumours compared to men. A previous study containing 496 patients showed a higher frequency of HPV-positivity among women but no statistical significance was seen (10). However, no conclusions could be taken in our study since the P16-status was not studied, but this could be a topic for further research to determine whether the treatment in some way can be optimized for the genders.

5.2 Recurrence

A recurrence rate of 17.6% was observed, this result match those seen in earlier studies (2, 29) although a higher frequency of distant recurrence was notified, with 51.6%, compared with about 25% seen in the literature (26). A higher incidence of recurrent inguinal lymph nodes was seen as well. This result may be explained by the fact that PET/CT has been seen to better detect metastasis, as described above. Known from previous studies, patients that relapse tend to do so within 18 months (36). In our study the mean was 17 months, with a range from 4-57 months, suggesting that the patients have a greater risk of recurrence during the first year after their treatment.

As seen in table 7 above, only 2 patients with a T1 tumour at the time of primary diagnosis had a recurrence, while a quite even distribution between T2-T4 was seen. This may suggest that the risk of recurrence is more correlated to the size of the primary tumour (i.e. aggressiveness) rather than pelvic lymph node spread, suggesting that the given radiotherapy burden should be more dependent on this factor. Despite limited comparability between studies due to different patients- and treatment factors, studies shows recurrence frequency ranging between 0 – 8.6% for early stage tumours (37). Wright et al. 2010 (26) found that for patients with a T1-T2 disease, 15% suffered recurrence compared to 42% of patients with a T3-T4 disease. These results further support the idea that in patients with small local tumours the adjuvant irradiated volumes may be decreased. This outcome is contrary to that of Leon et al. 2014 (2) who saw a high inguinal recurrence rate in the absence of adjuvant inguinal irradiation and thus suggest that inguinal lymph nodes should be irradiated even in T1 patients. It must be stressed, that in the current study the patients have undergone adjuvant pelvic lymph node irradiation whereby the recurrence rate would probably be higher if no radiotherapy had been given. This of course makes it difficult to draw clear conclusions.

Furthermore in table 7, it can be seen that 10 patients with lymph node negativity at the time for the primary diagnosis, developed a recurrence with metastatic spread (regional or/and distant). This result may also indicate for a benefit of prophylactic inguinal irradiation in patients with N0 tumours to avoid recurrence, which is consistent with recommendations in previous findings (3). However, to optimize these findings, the CVT-delineation for these patients should be examined in detail, to see whether the recurrence was in-field, (inadequate dose /positioning incorrect) or out-of-field (inadequate targeting). Previous studies have shown a 15% risk for recurrence in patients who did not receive elective inguinal radiotherapy in negative inguinal regions, showing the importance to treat N0 patients (38).

In summary, this suggests that the choice to irradiate inguinal lymph nodes should be based on the

size of the primary tumour, rather than inguinal metastatic spread and that also lymph node negative patients may benefit from this treatment.
There was no notable difference regarding anatomical locations of lymph nodes between the primary and recurrent patients.

5.3 Survival

In this study, a total of 27 patients died from malignancies, out of which 16 died of anal cancer. There is always a risk that what was suspected to be a primary tumour in fact were metastases from the anal cancer, and vice versa. It can be difficult to know whether it was the anal cancer or the other malignity that killed the patient. This opens up for uncertainty. Of course, some of the 6 patients with an unknown cause of death could have died of anal cancer, making it even more uncertain. However, all of the 27 patients mentioned above had a conclusive malignancy diagnosis documented in their medical records, which supports the death certificate. Unexpectedly many patients were seen to have lung cancer and vulvar cancer, where lung cancer killed six patients and vulvar cancer one patient. This was an expected result, since a significant higher prevalence of lung cancer and vulvar cancer among anal cancer patients compared to what would be expected in the normal population has been reported (2). Furthermore are these malignancy associated with smoking. Even though it was not studied how many of the patients smoked, these findings and findings from previous studies, may indicate that there is a relation. Smoking has been described as an independent risk factor for anal cancer and quit smoking has been found to reduce this risk (39).

The overall survival is showed in figure 2 and table 4 above. A previous Nordic study with 1266 cases showed a 3-years over-all survival for anal carcinoma at approximately 80%, which is consistent with our result. The same study also reported a statistical significant lower over-all survival for men. This is interesting since the same relation was seen in our series, but could not been proven statistically. One reason could be that the population sample was too small. Moreover, this could also be explained by the fact that men has a lower life expectancy and that the incidence seemed to peak at the higher ages for men in this study. Therefore, relative survival might have given us a better true picture here.
However, it is important to stress that these survival figures do not apply to the diagnosis of anal carcinoma as it is based only on the patients that have been treated with radiation therapy. Moreover, it is important to stress that the follow up time was not equal for all the patients, and that probably a higher rate of death would be seen if the follow-up time was equal, considering that a total of 17.6% of the patients had a recurrence.

5.4 Age

Median age has been seen to be around 60 years in previous studies (4, 28) studies which it comparable with 64 years seen in this study, thus not indicating on a shift on to younger ages. As seen in figures 1a and 1b above, the age frequency has a normal distribution, with a shift towards the older ages, as expected. One interesting finding was that the most common age interval for the total studied population, 66-70 years, is only true for the men. For the women, it was instead between 51-55 years the most patients got their diagnosis (n=25), but only one man got his diagnosis in this age interval. Instead, most men got their diagnosis between 56-66 years, while it for the women were more spread among the other age intervals. The incidence for men seemed to peak at the higher ages. At the same time, did not the mean and median ages differ between the genders. Reasons may be that the population sample was too small and that there was a big difference in ratio between men and women.

One interesting finding was that all the 3 women under 35 years were diagnosed within 6 months postpartum. This finding suggests that there may be a relation between development and growth of anal cancer and the boost of hormones during pregnancy. This would be an interesting aspect to assess in further research.

5.5 Study strenght and weakness

The studied population was quit large for this rare malignancy, increasing the statistical power. The cohort included a large number of patients in a short period of time (7 years), avoiding difference in treatment strategy and variation in the clinical staging of the patient. However, the current study had some limitations.

First of all, there was a big difference in size of population for men and women, which may affect the statistical analysis when comparing the genders. Even though the study population was quit large, we got small subgroups when dividing the patients by anatomical locations, thus increasing the insecurity. Optimal for further studies is to look at a much larger population, for example the Nordic countries or some European countries together.

When it comes to the performance of the PET/CT, it was done more routinely in the later years of the study. The sickest patients did not always undergo PET/CT and were thus excluded. It can be assumed that these patients had metastatic spread, which may affect the results. Even though the majority of the PET/CT was performed in Sahlgrenska, Gothenburg, some were done in Linköping. One source of weakness in this study that could have affected the results was that different radiologist assessed the PET/CT images, increasing the risk for measurements variations.

Histological conformation of the PET/CT results was not routinely done, with may lead to false upstaging or down staging.

It should be stressed that even though the current study aimed to study radiotherapy treatment, the majority of the patients have received chemotherapy. This could of course have affected the outcome for the patients and the adverse effects.

One of the major limitations of this study is that the adverse effects were based on medical records. Medical record studies are not optimal for this purpose since the adverse effects are not recorded in a structured way. This study only gathered the reported adverse effects even though some classifications were done in advance. Optimal would be to grade the side effects in severity and then in a structured way collect the information directly from the patients. This makes it hard draw any conclusions from the results in the current study. The rate of complications can be underestimated. Thus, the aim with this data collection in this study is more to act as an overview over how adverse effects are distributed and what kind of adverse effects the patients suffer from. This may give us an indication over how the patients' lives are affected by the treatment. James el al. 2013 (40) assessed adverse effects weekly during the first 1-8 weeks and haematological toxic effects were checked at week 11. In that study, the patients were reassessed in a structured and scheduled manner after the treatment. The adverse effects were in advance graded and defined based on current clinical guidelines. It would be beneficial if a similar prospective registration over adverse effects could be done regularly in the routine healthcare, for example in some kind of structured register. Of course, the focus then should be on some main adverse effects. During the radiotherapy treatment, it could be interesting to register grade of radiation dermatitis, number of loose stools per day, the patient's subjective experience of pain and to regularly perform a blood lab-status (hemoglobin, leukocytes and trombocytes). For the long term follow up it is suggested to register presence of anal continence, the patient's subjective experience of pain, sexual function/gynecological examination for women and the healing of the irradiated skin. An option would be that the patient himself grades his quality of life, which could give the oncologist possibility to follow the effects of the treatment, both in the short and long term.

6. Conclusions

The aim of this study was to map the anatomical localization of pelvic lymph node metastases at primary diagnosis of anal cancer based on findings from PET/CT. It was seen that patients with small tumours (stage T1) at time of primary diagnosis more seldom both had pelvic lymph node metastases and developed a recurrence. An increased risk of pelvic lymph node spread with greater size of the primary tumour was seen. These results may indicate that the irritated adjuvant volume may be decreased for small tumours, potentially decreasing morbidity for SCAAC patients. Since a recurrence is difficult to manage, it is thus suggested that adjuvant pelvic lymph node irradiation should stay as a recommendation for patients with T2+ tumours and with lymph node negativity.

Higher frequency of LNP seems to be seen in studies based on PET/CT compared to studies based on conventional techniques. Furthermore, our result indicates there may be a difference between some anatomical subsites. With this follows a risk for micro metastasis. This suggests that liaca externa should stay as a part of the adjuvant irradiation. Moreover, should mesorectal, iliaca interna inguinal and presacral lymph nodes should stay as a part of adjuvant radiotherapy volumes at well, at least for the bigger tumours (T2+) and/or N+. Size of the primary tumour and distant metastasis were seen being more important prognostic factors for the risk of developing recurrence. This suggests that the choice to irradiate inguinal lymph nodes should be based more on the size of the primary tumour and that even lymph node negative patients benefit from this treatment

However, further research needs to be done, preferably with a further focus on PET-CT and pelvic lymph nodes, before any changes in today's recommendations can be done.

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Populärvetenskaplig sammanfattning

Analcancer är en ovanlig cancersjukdom, med cirka 100 nya fall årligen i Sverige. Sjukdomen uppstår i analkanalen, vilket är de sista 4-5 cm av det långa rör vi kallar mag- och tarmkanalen. Analcancer börjar uppträda från 40 års ålder och är vanligast mellan 50-60 år. Sjukdomen är dubbelt så vanlig hos kvinnor som hos män. Trots att det fortfarande är en ganska ovanligt cancersjukdom har den blivit allt vanligare i västvärlden under de senaste decennierna.

Traditionellt har analcancer behandlats med kirurgi, d.v.s. att man opererar bort cancern. Under 80-talet upptäckte man dock att kirurgi inte hade några fördelar jämfört med behandling med cellgifter och strålning. Idag behandlas sjukdomen med en kombination av cellgifter och strålning. Cellgifter är en typ av läkemedel som skadar och dödar cancerceller. Vid strålbehandling, dödar man istället cancercellerna genom att stråla mot patienten. Operation är ett alternativ om patienten har kvar sin cancer efter behandlingen eller om cancersjukdomen kommer tillbaka.

Strålbehandlingen kommer att skada och döda cancercellerna. Tyvärr kommer även friska celler skadas och patienten kan komma att drabbas av biverkningar. Detta kommer att påverka patientens mående negativt. För att patientens ska kunna må så bra som möjligt både under och efter behandling strävar man hela tiden efter att försöka förbättra och effektivisera dagens behandlingsmetoder. Vid strålbehandling ger man behandling både mot själva cancern i analkanalen men även mot områden dit cancern kan sprida sig. Vanligast är att cancern sprider sig till körtlar kring ljumskarna. Dagens strålningstekniker har blivit allt mer precisa, för att på så sätt maximera strålningsdosen till valda områden och undvika att ”spilla över” på friska celler. Tack vare detta kan man minska biverkningarna, men samtidigt ställer det större krav på att man känner till området dit cancern kan sprida sig. Detta för att man inte ska riskera att behandla ett för litet område och istället missa spridd cancer som är för litet för blotta ögat.

Idag finns det rekommendationer kring vilket område i ljumskarna som ska behandlas. Samtidigt finns det också en osäkerhet över hur stort område som faktiskt behöver behandlas. Skulle man i vissa fall kunna utesluta vissa områden och på så sätt minska biverkningarna? Detta är vad denna studie har tittat vidare på.

I denna studie har PET-CT bilder från 166 patienter, som strålbehandlats på Sahlgrenska Universitetssjukhuset mellan 2010-2017, studerats. PET-CT är en typ av skiktröntgen där man, utöver att röntga, även sprutar in ett socker i patienten som kommer att leta upp och binda till cancerceller. Tack vare detta kan även små cancerförändringar hittas. På så sätt får läkarna en god och detaljerad bild av hur cancer har spridit sig och hur man ska behandla patienten på bästa sätt. I

studien studerades det om patienterna hade någon spridning till körtlar i ljumskarna och om det fanns någon spridning till andra organ i kroppen, t.ex. lever och lungor. Resultatet baserades både på röntgenbilderna och röntgenläkarnas skriftliga bedömning.

Denna studie har visat att man eventuellt kan minska strålningsområdet vid små analcancrar, och på sätt bespara patienter från jobbiga biverkningar, både på kort och lång sikt. Detta på grund av att endast en patient med en analcancer under två cm hade spridning till ljumskarna. Studien har också visat på att risken för att få ett återfall i sin analcancer mer verkar vara beroende på storleken på cancern i analkanalen och om patienten har spridning till andra organ i kroppen. Vanligast var det att analcancer spridit sig till levern. Det sågs också att ganska många patienter utan spridning till ljumskarna trots detta fick tillbaka sin cancersjukdom efter avslutad behandling. Detta kan betyda att även patienter utan spridning till ljumskarna kan gynnas av strålbehandling mot ljumskarna.

Det är fortfarande relativt få studier gjorda inom detta område och det behövs mer forskning innan några ändringar i dagens rekommendationer kan göras.